

A¹
another preferred embodiment of the oligonucleotide relates to a molecule whose nucleic acid sequence is partially complementary to the nucleic acid coding for the proto-oncogene bcl-2. In a particularly preferred embodiment, the oligonucleotide molecule according to the invention comprises the nucleic acid sequence 5'-GTT CTC CCA GCG TGT GCC AT-3' (SEQ ID NO:1).

Kindly substitute the fifth full paragraph on page 13 with the following:

A²
Figure 11: Chemical structure of the octreotate-PNA conjugate

The sequence of the base is: H-AGC GTG CGC CAT CCC-OH (SEQ ID NO:2).

Kindly substitute the part of the paragraph at the top of page 16 with the following:

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octreotide was produced by iodizing Tyr3 octreotide using the chloramine-T method according to Bakker et al., J. Nucl. Med. 9 (1990), 1501-1509. The resulting product was purified over HPLC and stored for further use at -80°C. The radioisotope Na¹²⁵I was obtained from Amersham Pharmacia Biotech (Freiburg, Germany). The complementary unmodified phosphodiester ODNs and phosphorothioate ODNs for the melting temperature analysis 5'-GTT CTC CCA GCG TGT GCC AT-3' (SEQ ID NO:1) (antisense) and 5'-ATG GCA CAC GCT GGG AGA AC-3' (SEQ ID NO:3) (sense) were synthesized according to standard methods.

Kindly substitute the last part of the paragraph on page 18 with the following:

Ad The ODNs exclusively containing phosphorothioate compounds 5'-GTT CTC CCA GCG TGT GCC AT-3' (SEQ ID NO:1) (antisense), 5'-ATG GCA CAC GCT GGG AGA AC-3' (SEQ ID NO:3) (sense) and 5'-TAC CGT GTG CGA CCC TCT TG-3' (SEQ ID NO:4) (non-sense) were synthesized by means of the β -cyanoethyl-phosphoroamidite chemistry in the 1 μ m range. The acetylation was carried out by means of 0.1 M acetic anhydride/tetrahydrofuran (THF) and 0.1 M imidazole/THF. The sulfurization was made by means of the EDITH reagents (3-ethoxy-1,2,4-dithiazoline-5-one). The commercially available thiol linker phosphoroamidite having a spacer of six carbon atoms (1-O-dimethoxytrityl-hexyl-disulfide-1'-[(2-cyano-ethyl)-(N,N-diisopropyl)]phosphoroamidite (Glen Research) was coupled to the 5' end. An acetonitrile wash step followed the last coupling. The resin was dried in an argon.

Kindly substitute the second paragraph on page 23 with the following:

Design:

As The peptide H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-OH (SEQ ID NO:5) (octreotate) was coupled with a PNA sequence which is complementary to the nucleotides -3 to +12 (region of the AUG start codon) of the Bcl-2 sequence. The sequence used is: H-AGC GTG CGC CAT CCC-OH (SEQ ID NO:2). Of this sequence a specific inhibition of the Bcl-2 protein synthesis was described (Mologni et al., Biochem. Biophys. Res. Commun. 264, pages 537-543 (1999)).

Kindly substitute the first paragraph on page 24 with the following: